CORRESPONDENCE

Re: Environmental Tobacco Smoke and Lung Cancer Risk in Nonsmoking Women

The report by Stockwell et al. (*1*) adds little to the data on environmental tobacco smoke and lung cancer. Various biases could have contributed to the associations noted between lung cancer and some indices of environmental tobacco smoke exposure. One concern relates to the use of healthy control subjects who were obtained by random-digit dialing, resulting in possible recall and nonresponse bias. Another concern, perhaps more so than in other lung cancer–environmental tobacco smoke studies, is information bias. Thus, all control subjects provided data directly, but surrogates provided data for 67% of case patients, many of whom were dead. There were also notable case–control differences in the proportions of interviews conducted face to face, by telephone, or by mail. Much attention has been given to bias from the misclassification of smoking habits (*2*), but, although Stockwell et al. (*1*) refer to this misclassification, they attempt no statistical adjustment and do not present a comparison of smoking status as recorded at various stages of their study. They also fail to consider confounding by diet. This failure is remarkable, since in another paper (*3*), apparently based on the same study, they report a strong protective effect against lung cancer among nonsmokers that is associated with total vegetable consumption and with intake of carotene, and, as I have reviewed elsewhere (*2*), a reduced consumption of vegetables is associated with marriage to a smoker. Adjustment for this source of bias alone could well render the reported association between lung cancer and exposure to environmental tobacco smoke not statistically significant.

There are also severe problems regarding presentation of results in the report by Stockwell et al. How can one update meta-analyses for differing indices of environmental tobacco smoke exposure when risk estimates are presented only for those indices for which an association is reported? What were the odds ratios and confidence intervals for environmental tobacco smoke exposure at work or during social activities? Meta-analysis would also be assisted by presenting, as other investigators do (*4,5*), numbers of cases and controls by exposure. Another difficulty is the unusual method of analysis for spousal environmental tobacco smoke exposure, with the referent group not, as is customary (*2*), married women whose husbands did not smoke, but instead women (married and unmarried) unexposed to household environmental tobacco smoke from any source. The relative risk estimate is thus not comparable with that for other studies (*2*). Furthermore, because of the strong association of the indices of environmental tobacco smoke used with both marital status and household size (the larger the family, the more likely is exposure), there are additional possibilities of confounding. The referent exposure group is identical for all analyses in Tables 2 and 3 of the report by Stockwell et al. (*1*); therefore, the cited risks for different indexes of environmental tobacco smoke exposure are not independent and could all be affected by an unusually low proportion of unexposed cases, perhaps resulting from recall bias.

In any event, the results of the study by Stockwell et al. (*1*) have no real effect on the overall data. Based on all data available before this study, meta-analysis (Table 1) gives no overall statistically significant association of lung cancer to workplace or childhood environmental tobacco smoke exposure and only a small positive association with a husband's smoking, which, as I have previously shown, can be explained in terms of misclassification of smoking habits, confounding, publication bias, and specific study weaknesses (*2*).

PETER N. LEE, M.A.
P. N. Lee Statistics and Computing Ltd.
17 Cedar Rd.
Sutton, Surrey SM2 5DA, England

References

(*1*) STOCKWELL HG, GOLDMAN AL, LYSAN GH, ET AL: Environmental tobacco smoke and lung cancer risk in nonsmoking women. J Natl Cancer Inst 84:1417–1422, 1992
(*2*) LEE PN: Environmental Tobacco Smoke and Mortality. Basel: S. Karger, 1992
(*3*) CANDELORA EC, STOCKWELL HG, ARMSTRONG AW, ET AL: Dietary intake and risk of lung cancer in women who never smoked. Nutr Cancer 17:263–270, 1992
(*4*) WALD NJ, NANCHAHAL K, THOMPSON SG, ET AL: Does breathing other people's tobacco smoke cause lung cancer? Br Med J (Clin Res Ed) 293:1217–1222, 1986
(*5*) NATIONAL RESEARCH COUNCIL: Environmental tobacco smoke. Measuring exposures and assessing health effects. Washington: Natl Acad Press, 1968
(*6*) FONTHAM ET, CORREA P, WU-WILLIAMS A, ET AL: Lung cancer in nonsmoking women: A multicenter case–control study. Cancer Epidemiol Biomarkers Prev 1:35–43, 1991
(*7*) LIU ZY, HE XZ, CHAPMAN RS: Smoking and other risk factors for lung cancer in Xuanwei, China. Int J Epidemiol 20:26–31, 1991

2nd Letter

Stockwell et al. (*1*) reported a relative risk of 1.6 for women who never smoked and who were married to smokers. This relative risk was adjusted for age, race, and educatio but not for other potential con

Table 1. Meta-analysis* of studies of environmental tobacco smoke and lung cancer amon reported lifelong nonsmokers

Source of environmental tobacco smoke exposure	No. of studies providing data	Relative risk estimates	95% confidence interval
Workplace	11	1.02	0.93-1.12
Childhood	11	0.96	0.85-1.09
Husband	30	1.19	1.09-1.31

*Based on data presented in (*2*) in Tables 3.14F, 3.21, and 3.23, with the addition of data f in two studies (*6,7*).

founders, such as diet, occupation, and prior lung disease. In fact, no mention was made of data having been collected on those factors. However, in another report, Candelora et al. (2) discussed an analysis of diet and lung cancer in a subset of subjects from the same study. Among their results, they reported strong inverse associations between lung cancer and both total vegetable consumption and total carotene intake. For example, the relative risk for the highest consumption quartile versus the lowest quartile was 0.2 for total vegetable consumption and 0.3 for total carotene intake. Although Calendori et al. stated that information was collected on occupation, exposure to known lung carcinogens, personal medical history, and family history of cancer and respiratory diseases, the diet analysis was not adjusted for any of those variables or for environmental tobacco smoke exposure.

Other studies (*3,4*) have noted inverse associations between dietary factors and lung cancer among people who never smoked, and three studies (*5-7*) have reported inverse associations between environmental tobacco smoke exposure and β-carotene intake among women in the United States who never smoked. Clearly, diet is an important potential confounder in reported associations between environmental tobacco smoke exposure and lung cancer. Since associations were reported between lung cancer and both environmental tobacco smoke exposure and diet in the report by Stockwell et al. (*1*), it would be interesting to know if there were associations between dietary factors and environmental tobacco smoke exposure that would give rise to confounding of the lung cancer associations. A multiple logistic regression analysis that considered all of the potential risk factors for which data were collected would be useful in elucidating these relationships.

A history of nonmalignant lung disease is another potential confounder in reported associations between environmental tobacco smoke exposure and lung cancer. In a large case–control study of women who never smoked, Brownson et al. (*8*) reported a spousal smoking–lung cancer relative risk of 1.0. This relative risk was adjusted for prior lung disease, but the extent of the adjustment was not stated. In another report on the same study, Alavanja et al. (*9*) estimated that 16% of lung cancer cases among women who never smoked were attributable to prior lung disease.

The importance of adjusting estimates of associations between environmental tobacco smoke exposure and lung cancer for potential confounders is emphasized by the weakness of the overall epidemiologic data. From a meta-analysis of the 13 currently available studies of U.S. women, including the studies by Brownson et al. (*8*) and Stockwell et al. (*1*), I have calculated a summary spousal smoking relative risk estimate of 1.07 (95% confidence interval = 0.95-1.21). This estimate was adjusted for smoking status misclassification, using the assumptions and methods of the U.S. Environmental Protection Agency (*10*). Only two of those studies (*8,11*) adjusted for prior lung disease, and none adjusted for dietary factors. Both Sidney et al. (*5*) and Le Marchand et al. (*6*) estimated that confounding by β-carotene intake could inflate environmental tobacco smoke-lung cancer relative risk estimates by about 10%; therefore, the very weak overall U.S. association could conceivably be explained by that single factor.

In a recent Journal editorial, Burns (*12*) asserted that a causal relationship between environmental tobacco smoke exposure and lung cancer has been established with what he characterized as "scientific certainty." The above considerations, and many other uncertainties in the environmental tobacco smoke-lung cancer epidemiology, lead me to believe that Burns' conclusion is unjustified.

MAXWELL W. LAYARD[1]
Layard Associates
2242 San Antonio Ave.
Alameda, CA 94501

References

(1) STOCKWELL HG, GOLDMAN AL, LYMAN GH, ET AL: Environmental tobacco smoke and lung cancer risk in nonsmoking women. J Natl Cancer Inst 84:1417–1422, 1992

(2) CANDELORA EC, STOCKWELL HG, ARMSTRONG AW, ET AL: Dietary intake and risk of lung cancer in women who never smoked. Nutr Cancer 17:263–270, 1992

(3) KOO LC: Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked. Nutr Cancer 11:155–172, 1988

(4) FRASER GE, BEESON WL, PHILLIPS RL: Diet and lung cancer in California Seventh-day Adventists. Am J Epidemiol 133:683–693, 1991

(5) SIDNEY S, CAAN BJ, FRIEDMAN GD: Dietary intake of carotene in nonsmokers with and without passive smoking at home. Am J Epidemiol 129:1305–1309, 1989

(6) LE MARCHAND L, WILKENS LR, HANKIN JH, ET AL: Dietary patterns of female nonsmokers with and without exposure to environmental tobacco smoke. Cancer Causes Control 2:11–16, 1991

(7) SHIBATA A, PAGANINI-HILL A, ROSS RK, ET AL: Dietary β-carotene, cigarette smoking, and lung cancer in men. Cancer Causes Control 3:207–214, 1992

(8) BROWNSON RC, ALAVANJA MC, HOCK ET, ET AL: Passive smoking and lung cancer in nonsmoking women. Am J Public Health 82:1525–1530, 1992

(9) ALAVANJA MC, BROWNSON RC, BOICE JD JR, ET AL: Preexisting lung disease and lung cancer among nonsmoking women. Am J Epidemiol 136:623–632, 1992

(10) ENVIRONMENTAL PROTECTION AGENCY: Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders. EPA/600/6-90/006B. Washington, DC, 1992

(11) GARFINKEL L: Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. JNCI 66:1061–1066, 1981

(12) BURNS DM: Environmental tobacco smoke: The price of scientific certainty. J Natl Cancer Inst 84:1387–1388, 1992

Note

[1]Author's note: The author is a partner in Layard Associates, a statistical consulting firm. He consults for the Tobacco Institute.

3rd Letter

While another investigator (*1*) sees the report by Stockwell et al. (*2*) as an affirmation of a discernible link between environmental tobacco smoke exposure and lung cancer, the evident inconsistencies pointed out in the Stockwell report should give one pause. For example, the adenocarcinoma data show no statistically significant relationship to environmental tobacco smoke exposure and no pattern of dose response, in sharp

2023513098

distinction to the large U.S. study by Fontham et al. (3) that reported an elevated risk only for adenocarcinomas. As a second example, the apparent relationship between the exposure information source and the reported risk is opposite to that reported in the large study by Garfinkel et al. (4). The point is that hunting expeditions through the data of an epidemiologic study can easily produce inconsistent artifacts where the exposure effects, if any, are likely to be very small.

My second point concerns the multiplicity of risk estimates in Table 2 of the Stockwell report, which were reported to be statistically significant. The impression some may have is that of repeated affirmations that strengthen the claim of a consistent effect. However, the reported risk estimates are overlapping. It appears that there may be only a single statistically significant result, i.e., the reported risk associated with non-adenocarcinomas with total exposure greater than 40 smoke-years. This single result can account also for reported statistical significance for all lung cancers, for adulthood exposure, for childhood exposure, and for all the related significant P values for trend. Furthermore, we were given no information regarding any possible association between childhood exposure and adulthood exposure.

Inevitably, choices were made in both the conduct of the study and the reporting of the data. It appears that some or all of the stated conclusions could be affected by inclusion, exclusion, or redistribution of a small number of cases. We should be told to what extent the investigators' choices could have affected such conclusions. Examples are choices related to geographic and temporal cutoffs for the selection of cases, the definition of exposure classes, the choice of adjustment variables and adjustment procedures, and grouping or splitting of cell types and respondent categories.

Ideally, science would be better served if the study protocols and reporting procedures were published in advance of data collection. The final report of the study could then distinguish between planned and unplanned material. Perhaps this Journal could help to promote such prestudy publication.

The possible impact of other potential biases in addition to the potential selection biases described above, deserve discussion. For example, smoker–nonsmoker misclassification errors were mentioned, but their impact was not assessed. Possibly of greater importance, there was no discussion of preferentially lower environmental tobacco smoke exposure among nonrespondent case patients or among case patients excluded because of inadequate information on active smoking.

It would have been helpful if Table 2 of the Stockwell report had included an additional column indicating how many cases fell into each of the exposure categories as well as the number unexposed. Such direct reporting of observed frequencies, while they are not demographically adjusted relative to the controls, provides a fuller appreciation of the underlying data.

Finally, the Stockwell report notes in a single sentence that the study also looked at environmental tobacco smoke exposure at work and during social activities and found no statistically significant estimated increase in lung cancer risk. This failure to report in detail is a fine example of a publication bias where practically no mention is made of a negative result, and it is therefore unlikely that this study would ever be included in a meta-analysis of workplace exposure studies.

PAUL SWITZER, PH.D.[1]
Department of Statistics
Stanford University
Stanford, CA 94305-4065

References

(1) BURNS DM: Environmental tobacco smoke: The price of scientific certainty. J Natl Cancer Inst 84:1387–1388, 1992
(2) STOCKWELL HG, GOLDMAN AL, LYMAN GH, ET AL: Environmental tobacco smoke and lung cancer risk in nonsmoking women. J Natl Cancer Inst 84:1417–1422, 1992
(3) FONTHAM ET, CORREA P, WU-WILLIAMS A, ET AL: Lung cancer in nonsmoking women: A multicenter case–control study. Cancer Epidemiol Biomarkers Prev 1:35–43, 1991
(4) GARFINKEL L, AUERBACH O, JOUBERT L: Involuntary smoking and lung cancer: A case–control study. JNCI 75:463–469, 1985

Note

[1]Author's note: These comments have been prepared at the request of the Tobacco Institute and represent the views of the author, not necessarily those of the Tobacco Institute or of Stanford University.

Response

In response to comments regarding the potential for dietary factors to confound the relationship between environmental tobacco smoke exposure and the subsequent risk of lung cancer (1), it is important to recognize that the possible role of dietary factors is important for both smokers and nonsmokers. The question being addressed in our report, however, was whether nonsmoking women who were exposed to environmental tobacco smoke had an increased risk of developing lung cancer compared with women who were not exposed. Our results indicated that exposure to environmental tobacco smoke can increase the risk of developing lung cancer in nonsmokers. A question that should be considered separately is whether dietary factors can exert a protective effect, i.e., reducing the risk of lung cancer among those exposed to tobacco smoke. Analysis of our data on this question is not yet complete, but the results should be available shortly.

It was suggested, in the correspondence by Layard, that prior lung disease may have contributed to the lung cancer risk in these women. As tobacco smoke is known to contribute to the development of both malignant and nonmalignant respiratory diseases in smokers, a shared common exposure to environmental tobacco smoke would appear a more likely explanation.

In the correspondence by Lee, the use of data from surrogate respondents was questioned. Because lung cancer is a rapidly fatal disease, the use of data from surrogate respondents was necessary in some cases. These data were presented in Table 3 of our report (1), showing the results

of analyses performed separately for self reports and for surrogate respondents. The odds ratios associated with environmental tobacco smoke exposure were actually greater when the analysis was limited to living subjects. This finding suggested that, had it been possible to interview all case patients directly, the data might have indicated an even stronger association between lung cancer risk and exposure to environmental tobacco smoke than they did when surrogate respondents were included. Lee also indicated that he considered it to be unusual to use women who had not been exposed to environmental tobacco smoke as the referent group because most previous studies had used only married women whose husbands had not smoked. Considering spousal exposure as the only source of household tobacco smoke, however, ignores the possibility of exposure from other household members. Janerich et al. (2) reported that exposures to high levels of household smoke during childhood and adolescence doubled the risk of lung cancer among nonsmokers. To consider only women married to a smoker as exposed, regardless of other reported exposures to smokers in the household, could result in the misclassification of exposed women as unexposed, possibly causing an artificial reduction in the odds ratio. Also, consideration of differences in household size, which could have an impact on the number of potential smokers in the home, did not vary by case or control status. Lee also stated that all associations between environmental tobacco smoke exposure and lung cancer from all available data can be explained by issues in study design. However, it must be noted that this study (*1*) increases the total number of studies with positive findings between environmental tobacco smoke exposure and lung cancer, and as these studies continue to be reported (*3*), dismissall of all such findings becomes increasingly difficult.

HEATHER G. STOCKWELL
ALLAN L. GOLDMAN
CHARLES I. NOSS
ELIZABETH C. CANDELORA
ADAM W. ARMSTRONG
Department of Energy
Office of Health
Germantown, Md.

References

(1) STOCKWELL HG, GOLDMAN AL, LYMAN GH, ET AL: Environmental tobacco smoke and lung cancer risk in nonsmoking women. J Natl Cancer Inst 84:1417–1422, 1992
(2) JANERICH DT, THOMPSON WD, VARELA LR, ET AL: Lung cancer and exposure to tobacco smoke in the household. N Engl J Med 323:632–636, 1990
(3) FONTHAM ET, CORREA P, WU-WILLIAMS A, ET AL: Lung cancer in nonsmoking women: A multicenter case–control study. Cancer Epidemiol Biomarkers Prev 1:35–43, 1991

Note

Correspondence to: Heather G. Stockwell, Sc.D., Department of Energy, Office of Health, EH-42, 19901 Germantown Rd., Germantown, MD 20874.